Rachel: Do you want to start?
Marisa: Sure. Today is Tuesday, June 14th.
Mo: June 14th.
Marisa: Rachel and I, Marisa are interviewing Professor Mo Khalil about synthetic biology and policies and practices.Could you please define the term “synthetic biology”?
Mo: That’s a hard question.
Rachel: We know!
Mo: I have a very simple definition, which I think covers most things that are being done in synthetic biology. I call it the engineering of complex biological systems from genetically modified organisms and that sort of practice of engineering these complex biological systems can be for the application of science the application of understanding the biological systems as well as for applications related to industry or medicine.
Marisa: Following up on that, what does synthetic biology mean to you?
Mo: Personally, I favor the use of synthetic biology as an approach as opposed to synthetic biology as a, sort of a discipline and why I think that’s important, I think that’s part of the issue, right? That it’s been distinguished from other parts of biology and genetic engineering as something totally different. I think it is different but I think it’s basically an approach. What I mean by that is...think about the analogy as to how proteins were studied. Protein structure-function. The elucidation of protein structure and then creating new structures and solving their structures and then understanding their functions, whereas synthetic biology is a similar idea, structure-function but just at the level of multiple proteins, multiple genes, a system. So, I really favor that sort of definition of synthetic biology as sort of this approach that both elucidating and utilizing these systems of interacting parts. Why I think that’s nice is it keeps it somewhat...it doesn’t necessarily make it out to be something alien, like some people think, you know?
Rachel: Could you please describe your field of work and why you are performing research in that field?
Mo: Yeah, sure. Along the lines of what I said is foundational understanding of biological systems and utilizing this new approach, right? This structure-function at the level of a system, right? We’re really interested in a few things. One is gene regulation, in eukaryotes primarily. I’m more interested in understanding how cells make decisions to turn on genes and turn off genes, right. That’s a very...what seems to be something very simple, right? That we’ve studied forever, but is actually a very complicated process. So we use synthetic biology as sort of this bottom-up approach to understand how this works. You can imagine, that the way biology is typically, you know, practiced is often times as through perturbation approaches, so knock-out. Things like that. So you take away something.
Rachel: Yes.
Mo: Or you knock it down, right? That will give you some insight into, sort of for instance, how genes are regulating each other, but it can only give you limited insight, in my opinion, if you’re really interested in the functionality of that system. And so an alternative way of studying that system is to construct bits of it. Either constructing pieces of it and perturbing it in those ways, or constructing fully artificial versions of those things. So, we really favor that approach where we construct fully artificial versions of things like transcriptional circuits and try to understand

how those transcriptional circuits respond to things in the environment to turn on genes, how those systems execute logic functions, how those systems execute, I would say more importantly than logic, dynamical things. Biology is a dynamic thing. All of these systems are basically executing very complex dynamical functions and we're really interested in elucidating these. So that's one area and then we have a number of general interests but that's sort of our bread and butter. Other interests happen to be utilizing tools from synthetic biology that solve certain problems and the one that we've become really interested in is antibiotic resistance. As you guys probably know from the news and everything that there's this huge problem that we're approaching a point where, maybe entering a post-antibiotic era where no antibiotic is going to be useful anymore because we've got bugs that have grown to resist everything. So we're thinking about new ideas about how you can use molecular tools and synthetic biology tools, sort of sensors and other things that can help address the problem with antibiotic resistance to get to the right therapy faster, quicker. And that's just one! We have a whole bunch of other projects but I'll highlight that one because I think it's a useful, easier one to understand.

Rachel: That makes sense.

Marisa: Why would you say the public should care about synthetic biology?

Mo: I think you should care about synthetic biology because I think there is potential for really great advances in a number of industries. I like the idea of synthetic biology to provide sort of tools and foundational ideas for creating, for making biology an engineerable substrate, right. So, we've done this with mechanical things, we've done this with electrical things, and chemical things right? But now we're entered an age where the living matter is the next substrate for engineering with very useful properties. The ability to sense things in different ways, the ability to adapt, right? And evolve! And we should harness those things for the creation of new technologies. I say that very vague. I say that very generally, but I think what's really interesting if you think about it that way is biology is this, sort of, new substrate then it can have impacts in lots of area. One of them being medical or therapeutic which, you know, everyone thinks about in terms of biology, but that's just one. I think if we can think about understanding how cells respond to things in the body and executing actions, you can develop new therapies, right? So things like cell-based therapies, which are fundamentally more interesting than small molecules, right? And being really utilized for things like cancer and regenerative medicine, right? Whereas small molecules will be not be able to, will hit some limitations, right? So, we're going to advance therapies in a very meaningful way, cancer and regenerative medicine are going to be the major ones there. But that's why, right? So, then you can think about new substrates for building materials, textiles, things like that, that are different than what we have and better for agriculture and the environment and things like that. I'm sure you'll ask me questions about GMOs. But I think there is a special...I think there is a huge need to begin to address the agricultural shortage with the population expansion and how we are going to feed the world. Also, sort of things that are tied to that, like water shortage. Anyway, I think that if you think of biology as yet another substrate for engineering, just like we think about resistors and things like that and mechanical things, then I think we just have more of a toolbox to play with is all.

Rachel: Phenomenal.

Mo: So, that's why I think the public should care about it.

Rachel: Alright. In terms of synthetic biology and genetic engineering, what do you feel the public is concerned about?

Mo: I think the number one thing that I think is a concern is...I think there are two main issues: one is this kinda ethical dilemma of "you're playing with life." You're tweaking life. You're playing God. I think there's, you know….Certain scientists haven't done a great job of pacifying the public by using statements like "we've now synthesized life," right? And I think those statements need to be very carefully made. So there's this kind of concern. I think there's really two: one is kind of this ethical thing of "You're playing God." You're manipulating and building life. Then there's this second thing which is safety. Ethics and safety. Safety kind of boils down to a couple things, like GMOs is a great example. In the absence of any sort of evidence or data on the safety of a GMO, it's assumed that it's not good for you or it's bad for you. Also, there's this assumption that whatever it is that we are making in the lab is going to get out and it's going to kill people or cause disease or whatever. And again in the absence of safeguards and discussions about this then I think I don't blame the public for having those types of assumptions.

Marisa: How do you make people, non-scientific people, interested in your work and what kind of interactions do you have with the non-scientific community?

Mo: Well, so I have limited interaction with the--no, that's not true. I have lots of interaction with the non-science world, but as an early-career scientist my job right now is to establish our work and do good science. That's my number one priority, is doing good science that will solicit funding, that's going to be appealing to my colleagues, and things like that that will help create the foundational tools to can then be potentially advanced. That said, because we are in this exciting new area, we do have some responsibility to discuss our work and be able to contextualize it and discuss its merits to a broader audience. Where I've done this is with reporters, for instance, when you put a piece out. I need to comment about somebody else's work, where we write kind of news and views for a broader audience where you have to explain or distill something that's kind of a more complicated topic in a meaningful way. And then just general forums. So I've been invited to do talks. One is called "A Pint of Science" and it's at a bar, beer-hour type thing and there's people from the science community and non-science community and we just talk generally about what you're doing and why you're doing it. So I would say in a more limited fashion compared to my more senior colleagues.

Rachel: Is your research publicly funded or funded privately by non or for profits?

Mo: Most of my research is publicly funded. So grants through NSF, NIH, Darpa. So federal funding. Those are the big three and they fund a lot of our work. I have a few small projects that are funded by industry through sponsored research and those projects are very specific. Industry is very interested in utilizing some of the tools that we're developing or helping...guide us in developing tools that could be useful for therapeutic applications and it's private money that way. I guess that's private. It still goes through the university, right.

Rachel: That makes sense. Alright.

Marisa: Would you say that you feel like you're receiving adequate funding for your research?

Mo: Yeah! So far so good! Funding has been, I think it's this thing that every researcher laments about because the budgets have been pretty stable and not growing. What that means is typically, the funding rates on grants has gone down as a result of that. So, in general, it has

been not the best climate for funding, but in our lab it's been good. It's been very good. We've been able to generate excitement about our work, and so yeah. Everything's been good.
Rachel: This is kinda going back again, but do you feel that you adequately reach out and inform the non-scientific community about your work?
Mo: That's a hard question. I feel like my job is to do good science. After we convey or portray the results of our stuff, after we write the paper, which is peer-reviewed, after which, my job is often to describe our work to a scientific or a non-scientific audience. And I feel like it is my job there to just as accurately as possible and as simply as possible, convey or portray our work. Beyond that, I don't find it my responsibility to reach out, to the public or a reporter or for any reason unless I'm getting solicitations or requests. And in that case, if I do get solicitations or requests, things like that, I am always happy and always accept those invitations. I try to be very active about that. So, I wouldn't say I necessarily go out of my way. Obviously in general, among the circle of people I talk with and friends are not in--I do my best to discuss our work in an understandable way.
Marisa: So, going a little bit back to that.
Mo: Sure.
Marisa: Do you feel like your research is protected from infringement? Does this impact your openness to discuss your work with the general population?
Mo: Yeah, so I saw this question. Now, what do you mean by infringement? Like, what's the
Rachel: Do you feel like your work is properly protected, like patents, or other people maybe taking credit for your work, or using a system that you don't want them using.
Mo: Ahh. So you're talking about intellectual property infringement.
Rachel: Intellectual property. Or even before, like you write a paper and you're working on something before things are patented, do you feel like your work is safe?
Mo: Well as a junior faculty, I'm always a little paranoid.
Rachel: That makes sense.
Mo: I'm always a little paranoid because this line of work is very fast. Things happen very quickly and so you're always a little reluctant to share kind of novel results before they're close to publishing, that's for sure. So this becomes somewhat of a strategic thing that I'm always balancing. Is the work ready? Am I relatively close to publication to sort of shop the work around as I go talk about it? Or is it just too early? And that will potentially give other people the chance to go out and--
Rachel: Jump on the wagon.
Mo: Yeah. So that's a general concern. You know it's something that I'm thinking about. And I just try to be strategic about it. So, for instance, now I'm getting close on some projects where I am, I'm talking about it. It's not protected. It's not published, but I feel like we're far enough along where it would be virtually impossible for anyone to come in and scoop it. And there's enough of...the way our work, unlike small molecules, or something like a protein where you solve a crystal structure or something like that, you put up the sequence or the molecule and that's it. It's out there. Here, I think the intellectual property is a much different model. It's really interesting. We're kind of exploring how these models really translate. And it's more of a sort of...there's an expertise involved in how to develop these modules or these systems. How you characterize and then demonstrate them. I think it's much more difficult for Joe Schmo or some

researcher to say, “Oh, yeah. The Khalil lab is working on this. I’m just going to replicate it or design a new one.” It’s more of a design process. So, to your general question, I have less concerns about the stuff I do than I would if I was working on an **???? (17:50)** looking for small molecule inhibitors or something like that. That said, we actively seek IP protection through the university. On certain projects which I think has really interesting potential for translation, the process that we follow is just basically, anytime I go and talk about it I leave, I don’t discuss details of sequences or things like that, and that’s on purpose because then, as we get close to publishing, with the Technology Development Office here at BU, we file for...we do an exploration of IP and then we typically file a disclosure which then gives us **???? (18:38) [a year of]** protection, after which you can opt to file for a patent or not. So, that’s a process I’m always thinking about if it’s a project that has interesting potential.

Rachel: So, you do, in general, feel like your property is well regulated?

Mo: Yes. Sorry, long winded answer. Yes, I do. I do.

Rachel: So BU does a good job of taking care of your lab, as far as infringements?

Mo: So far, BU has done a really nice job and we have at least one or two officers that’s been focused on our portfolio. So, they’ve done a really nice job at that. I’m in a situation right now, where there’s a company that we’re involved with that would like some tools and reagents and BU has come in as sort of the face, the legal face, and said “Here’s what we need you to do first, before we send any materials over.” So yes. So far, so good. My experiences have been positive.

Marisa: So, this is our last interview question.

Mo: Really? Oh wow. Yeah.

Rachel: Yeah, this one went so quick.

Mo: Good. So, have the other one's been more long winded?

Marisa: We’ve only had one other.

Rachel: Doug took over thirty minutes.

Mo: I can see that.

Rachel: And we managed to get on a lot of tangents, because whatever he said, I’d be like “I have a question about that.”

Mo: Ok, ok. Cool cool. But so far so good? This is all…

Marisa and Rachel: Yeah yeah.

Rachel: You’re giving us good information. It’s just an interview, Mo. You’re not interviewing for a job here.

Mo: Well anytime you turn on the video recorder, you know.

Rachel: It gets nervous. It’s just so we have notes for later so we don’t have to you know.

Mo: I know.

Marisa: What regulations do you feel should be placed on synthetic biology?

Rachel: Particularly in your area of research.

Mo: Oh boy.

Rachel: Or what ones do you like that already exist?

Mo: Well, you guys are doing some research now. So, what regulations are you aware of?

Rachel: The microbiology safety stuff. The recombinant DNA stuff. Chemical safety. Reagents.

Marisa: The RIMS stuff.
Mo: The classic stuff.
Rachel: Yeah, the classic things. So, I'm assuming you agree with all that.
Mo: Totally agree with all that. So, basically, this is a way of keeping databases of folks that are work in particular areas, like recombinant DNA and things like that and making sure you adhere to regulations and safety measures and I think that's all great. You know there is some of our work in BSL2 organisms and absolutely all of those regulations are critical and needed. Beyond that, I dont know. I would say in our lab we're not really exploring things that I think that are of any concern that would require additional regulations, but certain labs are. Certainly labs that are working in vectors that can replicate and potentially spread. You guys are probably looking a lot at gene drives and thinking about that problem. These are vectors that are designed to spread through populations of organisms. Certainly there...we may need to revisit regulations. My feeling is always that we have been genetically engineering bacteria and yeast. We've been genetically engineering cells for many, many years, even before synthetic biology. And there's not been any issues or concerns, right? And that's because, fundamentally anything that you engineer, unless it's these spreadable vectors and things like that, anything you engineer in the lab is going to be inherently more fragile than anything in the environment. I'll go out on a limb and say that. So this idea that any GFP expressing bacteria that you're going to engineer in the lab, you put it out there, the idea that it's going to potentially take over or spread I think is a little bit naive and probably not really an issue we have to worry about. So long as we adhere to the regulations for recombinant DNA and what you're allowed to synthesize. You know when you go and order oligos or genes from these companies they have really strict, algorithmic safety guards on what you're allowed to synthesize. Anything pops up on their filters, some toxic gene or something that's really bad, a gene or something like that, they'll flag it and they'll not allow you to buy it unless you have some real reasons. So I think there's some really good filters, even at the level of buying genes that prevent people from doing things that can cause problems. In our research, I don't see any need for revisiting any regulations that are beyond what's currently available for molecular biology and genetic engineering. As I said, I think there are some labs that are probably challenging the normal models, things like gene drive. People who work on stem cells or embryonic stem, they have their own concerns their and they have their own models there.
Rachel: That makes sense.
Mo: If you guys are looking for good examples or ideas of things that challenge the model, my lab's probably not that.
Rachel: It's kind of a shot in the dark. So you don't think any of these regulations should be lifted?
Mo: Lifted? Like the current ones? No. I think it's fair. I think any other molecular biology lab has to adhere to them and so should we.
Rachel: So I did have one question that popped up as I was listening to your answer to the last question.
Mo: Yeah, yeah. Sure, sure.
Rachel: So, generally synthetic biology falls under either the EPA, the FDA, or I think the NIH is the third one? Do you know which federal agency you have to adhere to and do you think that

because there's three completely different federal organizations that overhead all of synthetic biology, do you think that's klunky?

Mo: It is klunky. To my understanding, and I don't know what will be dealt here but from listening to policy people on this, yes. Nothing in our work has progressed to that point, but my understanding is that the system right now is klunky. Certainly advanced genetic engineering challenges some models. And so, where the FDA, for instance, is the regulatory body for drugs and things like that, what is the supervising role...which agency should supervise things like GMOs, agriculture? It's unclear. And right now, there's kind of workarounds. And so depending on what it is that you're doing or what you're thinking about, you could be at the FDA, you could be at the EPA, or you could even be somewhere else. I do think it's a little **???? (26:32)**, I do think it needs to be clarified. And I'll let the intermediate policy people, there's a person at MIT who knows quite a bit about this, think more about this. Where this is needed is, in my opinion, in enhancing or accelerating...things like therapeutics, cell-based therapies, rare diseases, cancers, things like that where your population sizes can be small, and these challenge the model of, for instance, FDA approval.

Rachel: There was an entire talk about that at the Mammalian Synthetic Biology

Mo: Yep, yep. Right there. That challenges the model. In my opinion it's a shame to go through the normal routes and stall drugs or therapies that could be really useful because they don't look like the normal model and their population size is small. And so I think in those cases, and as they described in Europe for instance, they're rethinking how this is done and I think we ought to do the same, to think a little more clearly about how these agencies work together or whether there's different channels for approval on these types of things.

Rachel: But, when you go through your stuff, do you go through the NIH to get approval for anything or do you not have to worry about--

Mo: We don't have to worry about this all that much

Rachel: Because it's all foundational?

Mo: Yeah, it's all foundational. But, if we do any animal studies for instance, when you talk to Wilson you can talk to him about this, there's a whole body here at BU that adheres to the regulations of, I think it's the NIH for animal practices. So our job is really to go through the board here at BU and detail out the protocols so that they ensure that we are ethically and properly doing experiments with animals and there is a good reason for it. All this stuff. So there's a really good pathway for that. So when you talk to Wilson, he'll elaborate more on that.

Rachel: Cool. He actually emailed us right at the beginning of this interview. "Do you guys want to talk today?"

Mo: Great.

Rachel: So that was good timing. Alright. That is our last question.

Mo: Fantastic!

Rachel: So thank you so much.

Mo: You're very welcome. I'm looking forward to seeing the synthesis of all this.

Rachel: Us too.